

Remarks

With this response, claims 1, 23 and 60 are amended. Support for these amendments can be found, for example, on page 17, line 16, on page 14, lines 4-15 and page 27, lines 19-20. New claims 75-79 are added. Support for claim 75 can be found, for example, on page 28, lines 2-3. Support for claims 76-79 can be found, for example, on page 4, line 2; on page 5, lines 14-15; on page 19, lines 15-20. Claims 59-70 have been withdrawn from consideration previously. Claims 51-58, 72 and 74 have been canceled previously without prejudice. Accordingly, claims 1-5, 7-11, 13-19, 22-25, 27-34, 36-44, 47-50, 71, 73 and 75-79 are pending and presented for examination.

No new matter is added by the present Amendment. Applicant specifically reserves the right to pursue the subject matter of the canceled or amended claims in a related application. Each of the rejections levied in the Office Action is addressed individually below.

Claim Rejection – 35 U.S.C. § 103

Claims 1-5, 7-11, 13-19, 22-25, 27-34, 36-44, 47-50, 71 and 73 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Wobus et al., J. Mol. Cell. Cardiol., 29:1525-1539, 1997 (“Wobus”) in view of Itskovitz-Eldor et al., Molecular Medicine, 6(2):88-95, 2000 (“Itskovitz-Eldor”); U.S. Patent Application 2003/0216812 (“Badylak”); Mooney et al., Biomaterials, 17:115-124, 1996 (“Mooney”) and Schuldiner et al., PNAS 97(21):1107-11312, 2000 (“Schuldiner”). The Examiner states that Wobus discloses that the growth factor retinoic acid accelerates mouse embryonic stem (ES) cell-derived cardiac differentiation and Itskovitz-Eldor teaches that human ES cells differentiate into embryoid bodies. In addition, the Examiner states that Schuldiner teaches biomolecules that direct differentiation of human ES cells into cardiac cells. The Examiner then cites Badylak as a primary reference for forming a 3D polymer matrix, and asserts that “it would have been obvious for one of ordinary skill in the art to replace the mouse ES cells of Wobus with human ES cells of Itskovitz-Eldor in the Badylak’s complex 3D-matrix comprising a polymer [...]” (Office Action, page 6).

As acknowledged by the Examiner, Badylak does not teach a 3D polymer matrix. Indeed, even if assuming that Badylak can properly be combined with Wobus and/or Itskovitz-Eldor, there is no teaching or suggestion in any of these references, or in any combination of them that relates to a 3D polymer matrix. The Examiner claims that these deficiencies are cured

by Mooney, which allegedly teaches a 3D polymer matrix made of poly(L-lactic acid) and poly(lactic acid-co-glycolic acid) (PLLA/PLGA). Applicant respectfully disagrees.

Badylak discloses a tissue graft construct comprising a liver basement membrane or processed collagen, whose *natural* composition and configuration provides a unique cell growth substrate. These matrices are often used in a *sheet* or *gel* form. Exemplary materials include MATRIGEL, ALLODERM, INTEGRA, APPLIGRAF, DERMAGRAFT and PERIGUARD (paragraphs [0004], [0005], and [0017]). However, those matrices are obviously incapable of resisting contractile forces exerted by stem cells in a 3D construct. One example is APPLIGRAF[®], which looks like a thin, circular piece of real skin (http://www.apligraf.com/patient/what_is_apligraf/what_is_apligraf.html).

By contrast, Mooney teaches stabilizing a 3D polyglycolic acid (PGA) fibre-based tubular device by spray-coating PLLA/PLGA and seeding endothelial cells and smooth muscle cells (*differentiated cells*) onto the stabilized tubes.

There would be no reason for one of ordinary skill in the art to combine Mooney and Badylak. Badylak does not teach or suggest anything about the desirability, let alone feasibility, of stabilizing its soft tissue graft to be a stiff polymer scaffold. In contrast to Badylak's matrices, the 3D tubular device taught by Mooney is (1) comprised of different matrices (synthetic *not* natural materials); and (2) designed for different properties (stable *not* soft). A skilled person reading Badylak would not be motivated to combine matrices with completely different materials and properties, and therefore would not be motivated to use a matrix as described by Mooney with Badylak's.

Besides, even if one were to assume that the skilled person would somehow apply the polymer coating of Mooney to Badylak's matrix, the teachings of these two references would lead to a tissue graft coated with PLLA/PLGA, which is neither explicitly nor implicitly taught to be porous matrix as recited in the claims.

Still further, as already noted, Mooney only discloses seeding and culturing *differentiated cells*, but not any *undifferentiated ES cells* on the tubular devices. Considering the state of the art in culturing and inducing differentiation of ES cells at the time of the inventions (even nowadays) was not so predictable that a skilled artisan would have a reasonable expectation of success in using Mooney's matrix alone, or in combination with Badylak's matrix for ES cell differentiation.

In addition, Wobus, Itskovitz-Eldor and Schuldiner, taken together or alone, provide no teaching for constructing a 3D cell support polymer matrix, let alone for seeding undifferentiated ES cells on such a matrix. Thus, Applicant submits that at least the presently claimed 3D polymer matrix is neither taught nor suggested by any of Badylak, Mooney, Wobus, Itskovitz-Eldor, Schuldiner, or any combination thereof.

Therefore, it would not have been obvious by the teachings of all the references for one of ordinary skill in the art to reach the claimed invention. Applicant respectfully requests that the rejection be removed.

Conclusion

For at least the reasons set forth above, the rejection in this case should be removed and the application should proceed to allowance. If, at any time, it appears that a phone discussion would be helpful, the undersigned would greatly appreciate the opportunity to discuss such issues at the Examiner's convenience. The undersigned can be contacted at (617) 248-5175.

Please charge any fees that are *necessary* to maintain pendency and/or protect the filing date of the present application to our Deposit Account Number 03-1721, referencing our Docket Number 0492611-0530.

Respectfully submitted,

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